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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/389,537	09/02/1999	PATRICK V. WARREN	DIVER1240-3	5543

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EXAMINER	
SLOBODYANSKY, ELIZABETH	
ART UNIT	**PAPER NUMBER**
1652	27

DATE MAILED: 06/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/389,537	WARREN ET AL.	
	Examiner	Art Unit	
	Elizabeth Slobodyansky	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *RCE request 18 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *24* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 18, 2003 has been entered.

The amendment filed March 18, 2003 amending claims 17-22, 28 and 29 and adding claims 30-43 has been entered.

Claims 17-43 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 17 and 18 have been amended to refer to "BLASTP" program. Examiner is unable to locate adequate support in the specification for said program. Claims 19 and 23 refer to "80%" identical enzyme. Examiner is unable to locate adequate support in the specification for 80% identity at amino acid level (see page 14, last paragraph). Claim 27 refers to enzyme that converts "about 400 μmoles of α-keto acid per minute per mg of the enzyme" whereas the specification describes "up to 400 μmoles" (page 22, last paragraph, emphasis added). Thus, there is no indication that said limitations were within the scope of the invention as conceived by Applicants at the time the application was filed.

Accordingly, Applicants are required to cancel the new matter in the response to this Office Action.

Claims not specifically discussed above are rejected as dependent from the rejected claim.

Claims 17-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 17-27 are drawn to transaminase or aminotransferase with any donor-acceptor and stereo specificity having an amino acid sequence which is at least 70% (or 80%, 90%, 95%) identical to any one of SEQ ID NOs: 25-32.

The term "transaminase or aminotransferase" describes the generic function of diverse classes of enzymes having different substrate and stereo specificity with regard to the amino group donor and acceptor. While enzymes having amino acid sequences of SEQ ID NOs: 25-32 are aminotransferases or transaminases with a known specificity, it is unknown what specificity will have an aminotransferase having an amino acid sequence that is at least 70% identical to said sequences. Therefore, the claims are to or depend from a diverse genus of functionally different proteins.

The putative activity of enzymes having the amino acid sequences of SEQ ID NOs:25-32 is based on the homology with other enzymes (pages 4-5; pages 7-8, Table 1). This homology is on average about 40%. An enzyme with 70% identity will have less than 30% homology to the known sequence. The enzymes to which SEQ ID NOs: 25-32 are homologous may have different donor-acceptor and stereo specificity. The correlation between the structure and the specific transaminase/aminotransferase function is not disclosed in the specification nor is known in the art. Therefore, it is unpredictable what will be the specific transaminase/aminotransferase function of a protein having an amino acid sequence that is at least 70% homologous to SEQ ID NOs: 25-32. The specification does not disclose identifying characteristics which would

allow to distinguish an aminotransferase of a defined donor-acceptor and stereo specificity from another aminotransferase specific for a different donor-acceptor pair.

The specification discloses only a single species within the genus i.e., transaminase/aminotransferase of any one of SEQ ID NOs:25-32 which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Thus, transaminase or aminotransferase of an unknown specificity towards donor and acceptor of the amino group and having an amino acid sequence which is at least 70% identical to SEQ ID NOs 25-32 lacks sufficient written description.

Claims 17-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a specific transaminase/aminotransferase having an amino acid sequence as set forth in any one of SEQ ID NOs: 25-32, does not reasonably provide enablement for a transaminase or aminotransferase with an undefined specificity having an amino acid sequence at least 70%, 80%, 90% or 95% identical to any one of SEQ ID NOs: 25-32 and for a specific transaminase or aminotransferase having an amino acid sequence at least 70% identical to any one of SEQ ID NOs: 25-32 and methods of use thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7)considered in determining whether undue experimentation is required, are summarized the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claims 17-27 are drawn to a transaminase/aminotransferase with any specificity with regard to the amino group donor and acceptor and a method of use thereof. Despite knowledge in the art to produce mutations in proteins and the isolation of DNA molecules, the specification fails to provide guidance as to where, and what type of (i.e., what amino acid to substitute into, add to and/or delete from the known sequence), changes in amino acid residues will result in an unspecified aminotransferase activity. Therefore, the breadth of these claims is much larger than the scope enabled by the specification.

The state of the art does not allow the predictability of the properties based on the structure. The amino acid sequence of a protein determines its structural and functional properties and knowledge of which residues can be altered or removed, so that they retain 70% identity, and result in an unspecified aminotransferase activity is

well outside the realm of routine experimentation. Since the state of the art does not allow the predictability of the properties based on the structure, it is unpredictable what will be the specific function i.e., donor, acceptor and stereo specificity of transaminase or aminotransferase with the amino acid sequence at least 70%, 80%, 90% or 95% identical to SEQ ID NOs:25-32.

Claims 28-43 are drawn to transaminase or aminotransferase with defined donor-acceptor specificity having an amino acid sequence at least 70% identical to any one of SEQ ID NOs: 25-32 and a method of use thereof.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any sequence that is at least 70% identical to any one of SEQ ID NOs: 25-32 because the specification does **not** establish: (a) regions of the protein structure which may be modified without effecting each specific aminotransferase activity of each polypeptide of SEQ ID NOs: 25-32 of the instant invention; (B) the general tolerance of said polypeptide to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining each specific requisite transaminase or aminotransferase function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by

the instant claims, and the positions within a protein's sequence where modifications can be made with a reasonable expectation of success in obtaining the desired activity. The specification fails to provide guidance for the selection of which of the infinite number of variants have the specific requisite activity.

Furthermore, with regard to claims 18 and 23-27, drawn to a method for transferring an amino group from an amino acid to an α-keto acid using transaminase or aminotransferase with a sequence at least 70%, 80%, 90% or 95% identical to any one of SEQ ID NOs: 25-32, the specification teaches that "transaminase can catalyze stereoselective synthesis of D- and L-amino acids from their corresponding α-keto acids" (page 22, emphasis added). The specification provides no guidance as to how to use any one of SEQ ID NOs 25-32 for the synthesis of D- and L-amino acids other than for which they are specific. Furthermore, SEQ ID NOs: 27, 30 and 31 do not appear to have the requisite function for transferring an amino group from an amino acid.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including transaminase or aminotransferase having an amino acid sequence at least 70%, 80%, 90% or 95% identical to any one of SEQ ID NOs: 25-32 and having any transaminase/aminotransferase activity as well as specific transaminase or aminotransferase having an amino acid sequence at least 70% identical to any one of SEQ ID NOs: 25-32 and methods of use thereof. The scope

of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 17-43 are directed to or depend from an enzyme with transaminase or aminotransferase activity, either undefined or specific. The scope of the term "an enzyme with activity" is unascertainable because it is unclear what are enzymes other than transaminases or aminotransferases that are included in the scope of the claim.

Amending the claims to recite "a polypeptide" with a transaminase or aminotransferase activity would obviate this rejection.

Claims 28-43 recite specific transaminases or aminotransferases. Some of said specific activities are not defined in the specification or readily known in the art. For example, it is not defined which reaction is catalyzed by an enzyme of SEQ ID NO:27, 28, 30, 31. Furthermore, it is not defined and is unclear what is the difference between

various aspartate aminotransferase or transaminase activities of SEQ ID NOs: 25, 26, 29. Further, it is unclear what is the difference between various aspartate aminotransferase or transaminase activities of SEQ ID NOs: 25, 26, 29 and activity of SEQ ID NO:32. The search of Enzyme nomenclature database reveals that "aspartate transaminase" is named "aspartate aminotransferase" and "transaminase A". Further, "branched-chain amino acid aminotransferase" is synonymous with "transaminase B". Without knowing what activity is implied, it is impossible to ascertain the metes and bounds of the claims.

Response to Arguments

Applicant's arguments filed March 18, 2003 have been fully considered but they are not persuasive.

Applicants argue that "the skilled artisan would understand that transaminases or aminotransferases are enzymes that can transfer a nitrogenous group from a donor to an acceptor such as catalyzing the transfer of an amino group from an amino acid to an α-keto acid. Therefore, the skilled artisan would understand that the enzymes will require an amino acid and an α-keto acid as substrates, both of which the skilled artisan would recognize" (Remarks, page 8). This is not persuasive because while artisan would know what is an amino acid, an α-keto acid and transaminase, each of these generic terms encompasses a great number of compounds. It is unknown what is

the correlation between the structure that is 70%, 80%, 90% or 95% identical to any of the SEQ ID NOs: 25-32 and any specific transaminase activity. For example, a genus of transaminases that are 70%, 80%, 90% or 95% identical to SEQ ID NO:25 is represented by a single transaminase of SEQ ID NO:25 that is aspartate aminotransferase (similarly, for SEQ ID NOs: 26-32). Further, "Applicants have named eight representative aminotransferases to describe the genus. The scope of the claimed invention, however, does not encompass just any enzymes, only those that have aminotransferase activity and that have at least 70% sequence identity to SEQ ID NOs: 25-32" (page 8). This is not agreed with because the genus of transaminases encompasses enzymes with widely different functions and because of that, a functional characteristic such as "transaminase activity" is insufficient. The vast genus of transaminases encompasses several subgenera with a specific activity, each of which is represented at best by a single structure. Applicants assert that "It would, therefore, be onerous for the Applicants to list every possible reaction that the enzymes may catalyze and unnecessary for skilled artisan to practice the claimed invention" (page 8). This is not agreed with because Applicants are not required to list every possible reaction that the enzymes may catalyze but only the reaction that defines their specificity. It is known that not all enzymes have only one substrate but defining the activity does not mean that. For example, it is known that "branched chain aminotransferase activity" acts not only on leucine but also on isoleucine and valine.

With regard to the enablement, Applicants argue that "it is well within the knowledge of the skilled artisan to introduce mutations in proteins and to isolate DNA molecules" and "to identify those enzymes whose function is that of transaminase or aminotransferase, such as transferring an α-amino group from one amino acid to an α-ketoglutarate" (page 9, emphasis added), and similarly on page 11). This is not persuasive because in the instant case, the activity is not limited to transferring an α-amino group from one of twenty naturally occurring amino acids to an α-ketoglutarate as discussed in the specification on pages 1-2 but includes transferring an α-amino group from any amino acid, both naturally-occurring and man made, to any α-keto acid not only α-ketoglutarate. Furthermore, while methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan producing variants as claimed by applicants requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the claimed property. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute **undue** experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification.

Applicants further argue that "one of skill in the art would have been able to determine any possible transaminase or aminotransferase activity of an enzyme" (page 11). The examiner agrees that one of skill in the art would have known how to determine a specific defined transaminase activity. For example, one of skill in the art would have known how to determine a specific defined transaminase activity of transferring α-amino group of the 20 L-amino acids to the α-carbon atom of α-ketoglutarate (the specification at page 1, last paragraph; page 21, penultimate paragraph, and page 22, penultimate paragraph). However, the examiner disagrees with the notion, for the reasons discussed above, that one of skill in the art would have known how to determine any possible transaminase or aminotransferase activity.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner

May 30, 2003